DETAILED ACTION

1. Applicant's amendment and response filed 11/18/10 and Applicant's response filed 1/18/11 are acknowledged and have been entered.

2. Applicant's election without traverse of Group II (claims 7-16) in Applicant's response filed 1/18/11, and species of SEQ ID NO: 1 and BMP-7 in telephonic interviews with Mr. Stephen Todd on 2/8/11 and 2/11/11 is acknowledged.

Claims 7-16 read on the elected species.

Accordingly, claims 1-6 (non-elected Group I) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Upon consideration of the prior art, the SEQ ID NO: 2-5 are also included in examination.

Claims 7-16 are currently being examined.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the priority claim for benefit of PCT/US04/34679 is under 35 USC 119. It should be under 35 USC 120.

4. The use of the trademarks PEPSETS, MIMOTOPES, CELL-DYN, MICROBETA and LYMPHOPREP have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.
Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 11 recites the limitation "said epitope region" in line 1. There is insufficient antecedent basis for this limitation in the claim, as ultimate base claim 1 recites "peptide comprising said T-cell epitope".

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 7-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/077187 A2 in view of admitted prior art on page 27 of the description at lines 20-25 (Walker and Wright., Neurosurg. Focus 13(6): 1-13, 2002) and Paul (Fundamental Immunology 4th Edition, 1999, page 12, Lippincott-Raven Publishers, Philadelphia/New York), as evidenced by an admission in the specification on page 32 at lines 14-19 and on page 35 at Table 1.

WO 02/077187 A2 teaches producing altered proteins comprising a T cell epitope that is altered to make it non-immunogenic or less immunogenic. WO 02/077187 A2 further teaches that the alteration may occur by making amino acid substitutions to corresponding amino acid residues of a homolog of the protein of interest.

WO 02/077187 A2 teaches that the epitope may be determined by a method that comprises obtaining from a single blood source a solution of dendritic cells and a solution of naïve CD4+ and/or CD8+ T cells, promoting differentiation in said solution of dendritic cells (such as for instance using two cytokines GM-CSF and IL-4), combining said solution of differentiated dendritic cells and naïve T cell with said protein, and measuring the T cell proliferation. WO 02/077187 A2 teaches that instead of using the protein of interest in the said method, using a series of peptide oligomers which correspond to all or part of the protein of interest, *i.e.,* a PEPSET, and when the T cell epitope peptide is identified, an altered peptide may be created by altering the amino acid resides of the epitope until the peptide produces a different, reduce T cell response, or no response in comparison with the unaltered sequence. The amino acid substitution(s) can include a portion of a homolog of the protein of interest. Alteration can also include amino acid residue deletions or additions in the epitope of interest. The substitution may also include amino acid residues that maintain a specific structure, such as an alpha-helix or a beta-sheet structure (*i.e.,* the art teaches the limitation recited in instant claim 9 "wherein said T-cell epitope is modified by substituting a portion of the amino acid sequence of said T-cell epitope with a sequence which substantially mimics the major tertiary structure attributes of said T-cell epitope."). WO 02/077187 A2 teaches that the peptides can be either 10-mer or 15-mer peptides overlapping by 3 amino acid residues(see entire reference, especially detailed description, page 5 at lines 1-26, page 10 at lines 5-35, page 11 at lines 22-35, page 12 at line 1-24, examples 2-5).

WO 02/077187 A2 does not teach production of altered BMP proteins, including BMP-7.

Admitted prior art Walker and Wright teach that BMP has been administered to assist in correcting spinal problems in certain patients; however, a significant proportion (about 38%) of these patients develop detectable anti-BMP antibodies, *i.e.,* they produce antibodies against a naturally occurring endogenous human protein. Walker and Wright teach "such antibody formation is worrisome. At a minimum, antibody formation likely limits future treatments with the same BMP subtype in patients in whom antibodies are detected. Subsequent exposure to the same antigen would likely induce a significant immune response." (especially abstract and section bridging columns 1-2 on page 10).

Paul teaches that CD4+ T helper cells are cells that stimulate B cells to make antibody (section at column 2 on page 12).

The admission in the specification on page 32 at lines 14-19 and on page 35 at Table 1 is that SEQ ID NO: 1-5 are 15-mer peptides from BMP-7 protein that were produced when making overlapping 15-mer peptides that overlap by 3 amino acid residues.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced altered BMP protein, including BMP-7 taught by the admitted prior art Walker and Wright, using the methodology taught by WO 02/077187 A2, and including using a PEPSET that includes one or all of SEQ ID NO: 1-5 (see below) and testing for reactivity of the peptides to CD4 + T cells, and additionally to CD8+ T cells (*i.e.,* CTL).

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce a form of BMP-7 that has reduced immunogenicity for use in the patients who produce antibodies against the native BMP protein, and to test for potential CTL reactivity.

Instant claims 11 and 16 are included in this rejection because SEQ ID NO: 1 is a 15-mer peptide that is produced from BMP-7 protein when making overlapping 15-mer peptides that overlap by 3 amino acid residues, as evidenced by an admission in the specification on page 32 at lines 14-19, *i.e.,* that full length amino acid sequence of BMP-7 and BMP-14 were used to create 15-mer peptide sets with adjacent peptides sharing 12 amino acid residues, and on page 35 at Table 1, which shows that SEQ ID NO: 1-5 are from BMP-7. The primary art reference teaches making overlapping 15-mer peptides with 3 amino acid residue overlap, and the secondary reference teaches BMP-7. Thus, the combined references teach making overlapping 15-mer peptides from BMP-7 with 3 amino acid residue overlap, which peptides include SEQ ID NO: 1-5. Therefore, although the art references do not *explicitly* teach SEQ ID NO: 1-5, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an

unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F2d 1252, 195 USPQ 430 (CCPA 1977).

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Phuong "Neon" Huynh, can be reached on 571-272-0846. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644